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SCIENTIFIC DATA REVIEWS
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 19 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Difenconazole (Dividend™) - Worker Risk Assessment for Use as a Seed Treatment to Control Cereal Diseases

FROM: Elizabeth A. Doyle, Ph.D. E.A. Doyle 7/15/94
Registration Section
Chemical Coordination Branch (7509C)

TO: Cynthia Giles-Parker, PM-22
Registration Division (7505C)

THRU: Albin Kocialski, Ph.D., Section Head ABK
Registration Section
Chemical Coordination Branch (7509C)

and

Debra F. Edwards, Ph.D., Chief Debra Edwards 7/18/94
Chemical Coordination Branch
Health Effects Division (7509C)

Action Requested: Calculation of worker risk from short term (≤ 7 days) and intermediate term (7 to 90 days) exposure.

Introduction: Difenconazole, is a systemic fungicide for the control of a variety of soil and seed borne diseases of wheat and spring barley. Formulated as Dividend™, Difenconazole is applied to seed as a water-based slurry through standard slurry or mist-applied commercial seed treaters at the rate of 1 fl. oz/100 lbs. seed.

Worker Exposure: No worker exposure data were provided by the registrant for this registration. Therefore, OREB has used data for Apron™ Flowable, a similarly applied product, as surrogate for Dividend™ for estimation of the potential worker exposure ("Less Than Lifetime" Exposure for the Active Ingredient Difenconazole Used as a Seed Treatment to Control Cereal Diseases, B. F. Kitchens to C. Giles-Parker, July 13, 1994).

OREB indicated that the application of Apron™ is substantially similar to that of Dividend™ with the exceptions that 1) Apron™ is applied at a maximum rate of 2 fl. oz./100 lbs. seed where Dividend™ is applied at a maximum rate of 1 fl. oz./100 lbs.

seed, and 2) Apron™ is a wettable powder where Dividend™ is a liquid formulation. OREB indicates that, in their experience, liquid formulations result in lower worker exposures than wettable powders.

Combined inhalation and dermal geometric mean exposures from the Apron™ ranged as follows:

Mixer/operator	-	0.001 - 0.014 mg/kg/day
Bagger	-	0.002 - 0.010 mg/kg/day
Bag sewer	-	0.008 - 0.017 mg/kg/day

OREB indicates that worker exposure during the treatment and packaging of seed would fall into the time frames defined by the HED Less than Lifetime assessment periods.

Toxicology Endpoints: The Less than Lifetime Committee of HED has identified endpoints for risk assessment for two occupational time frames: 1) exposures of 7 days or less duration, and 2) exposures of 7 days to several months duration (Toxicology Endpoint Selection Document attached).

For a short term exposure (7 days or less), the endpoint selected for risk assessment is a NOEL of 25 mg/kg/day from a developmental toxicity study in rabbits, with a LOEL of 75 mg/kg/day based upon increased postimplantation loss and resorptions and a significant decrease in fetal weight.

For longer term exposures (7 days to several months), the endpoint selected for risk assessment is a NOEL of 1.25 mg/kg/day from a 2-generation reproduction study in rats, with a LOEL of 12.5 mg/kg/day based upon decreased pup weights at day 21.

Risk Assessment: MOEs were calculated using the toxicology endpoints in conjunction with the high end of the exposure ranges for each occupational task.

MOEs were calculated as:

NOEL from toxicology study/high end exposure estimate = MOE.

MOEs for each task are summarized below.

	7 days or less	7 days to several months
Mixer/operator	1785	89
Bagger	2500	125
Bag sewer	1470	74

As indicated in the OREB exposure assessment, exposure estimates were obtained using data from Apron™, a similarly applied seed

treatment because data were not available for Dividend™ per se. Data from Apron™ may be anticipated to produce exposure estimates higher than likely to be seen with Dividend™ because 1) Apron™ is applied at twice the rate of Dividend™ and 2) Apron™ is formulated as a wettable powder where Dividend™ is formulated as a liquid; in OREB's experience, wettable powders result in higher exposures than liquid formulations. In addition, a default assumption of 100% dermal absorption was used because no other data were available. Dermal absorption is highly unlikely to be this high. As a result, MOEs reported above may be artificially lowered due to an overestimate of exposure and dermal absorption.

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

TO: James Kariya, DRES
Larry Dorsey, OREB
Esther Saito, CBTS
Caswell File
Debra Edwards, CCB
Edward Zager, CBRS
William Burnam, SAB
George Ghali, RfD Secretary

Chemical Name: **DIFENOCONAZOLE**

PC Code: **128847**

Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Reviewer: _____ Date: 9/13/94

Branch Chief: _____ Date: 6/17/94

Dermal Absorption Data (If available):

None available

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Acute Dietary Risk (Endpoint, One Day)

Study Selected - Guideline No.: 83-3(b)

MRID No.: 420900-17

Summary (Enter Standard Executive Summary or equivalent): In a developmental toxicity, impregnated rabbits [16/dose] were given oral administration of difenoconazole at 0, 1, 25, or 75 mg/kg/day during days 7 through 19 of gestation. At 75 mg/kg/day, maternal toxicity was manifested as decreased body weight gain and food consumption; no maternal toxicity was observed at lower doses. Developmental toxicity observed only at 75 mg/kg/day was a slight nonsignificant increase in postimplantation loss and resorption/doe and a significant decrease in fetal weight. **For maternal toxicity, the LOEL of 75 mg/kg/day is based on decreases in body weight gain and food consumption; the NOEL is 25 mg/kg/day. For developmental toxicity, the LOEL of 75 mg/kg/day is based on increases in postimplantation loss and resorptions and decreases in fetal body weight; the NOEL is 25 mg/kg/day.**

Endpoint and dose for use in risk assessment: Postimplantation loss and resorption/doe and a significant decrease in fetal weight; LOEL = 75 mg/kg/day; NOEL = 25 mg/kg/day.

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Short Term Occupational or Residential Exposure (1 to 7 Days)

Study Selected - Guideline No.: 83-3(b)

MRID No.: 420900-17

Summary (Enter Standard Executive Summary or equivalent): See above [Acute Dietary Risk]

Endpoint and dose for use in risk assessment: See above [Acute Dietary Risk].

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Intermediate-Term Occupational or Residential Exposure (1 Week to Several Months)

Study Selected - Guideline No.: 83-4

MRID No.: 420900-18

Summary (Enter Standard Executive Summary or equivalent): In a two generation reproduction study, difenoconazole was administered in the diet to male and female rats at 0, 25, 250, or 2500 ppm [0, 1.25, 12.5, or 12.5 mg/kg/day, respectively]. Statistically significant reductions in body weight gains of F_0 and F_1 males were observed at 2500 ppm during Days 70-77 and during the course of the study [terminal body weight minus Day 0 body weight]. Significant reductions in body weight gains of F_0 and F_1 females were seen during the pre-mating, gestation, and lactation periods. A dose-related, but non-statistically significant decreases in body weight gain was seen in F_0 females at 250 ppm during Days 70-77 prior to mating, Days 0-7 of gestation, and Days 7-14 of lactation. At 2500 ppm, significant reductions in pup body weight were detected on Days 0, 4 [pre- and post culling], 7, 14, and 21 for males and females of both generations. There was a significant reduction in the body weight of F_1 male pups on Day 21 in the 250 ppm group. The percentage of male pups in the F_1 generation surviving Days 0-4 was significantly reduced in the 2500 ppm group. **For parentalt toxicity, the LOEL of 250 ppm [12.5 mg/kg/day is based on the decreased maternal body weight gain; the NOEL is 25 ppm [1.25 mg/kg/day. For reproductive toxicity, the LOEL of 250 ppm [12.5 mg/kg/day] is based on decreased pup weights at Day 21; the NOEL is 25 ppm [1.25 mg/kg/day].**

Endpoint and dose for use in risk assessment: Decreased pup weight at Day 21 at 250 ppm [1.25 mg/kg/day].

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Cancer Classification and Basis: Group C; Possible Human Carcinogen based on statistically significant increases in liver adenomas, carcinomas, and combined adenomas/carcinomas in both sexes of CD-1 mice, only at doses which were considered to be excessively high for carcinogenicity testing.

Q_1* = None

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R_fD and basis: An RfD of 0.01 mg/kg/day was derived using a NOEL of 0.96 mg/kg/day and an uncertainty factor of 100 for inter-and intra-species variation; the NOEL was established from a 2-year feeding study in rats. The LOEL, based on hepatotoxicity, is 24.12 mg/kg/day in males and 32.79 mg/kg/day in females.

NOEL for critical study: 0.96 mg/kg/day

Study Type - Guideline No.: 83-1 and 83-2(a)

MRID: 420900-19; 427100-10

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Chemical:	**Difenoconazole**
PC Code:	***128847***
HED File Code	**14000 Risk Reviews**
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HED Records Reference Center
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